

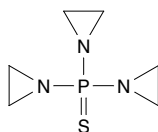
Thiotepa

CAS No. 52-24-4

Known to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as tris(1-aziridinyl)phosphine sulfide



Carcinogenicity

Thiotepa is *known to be a human carcinogen* based on sufficient evidence from studies in humans. Thiotepa was first listed in the *Second Annual Report on Carcinogens* in 1981 as *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals and insufficient evidence of carcinogenicity from studies in humans. Thiotepa was reclassified as *known to be a human carcinogen* in the *Eighth Report on Carcinogens* in 1998.

Cancer Studies in Humans

Exposure to thiotepa is specifically associated with leukemia in humans. Adamson and Seiber (1981) summarized nine case reports from 1970 to 1978 of secondary development of nonlymphocytic leukemia in patients with primary cancer at other sites who had received only thiotepa as a therapeutic agent. Additional evidence was provided by a case-control study which found that patients treated with thiotepa were significantly more likely to develop secondary leukemia than those undergoing surgery alone (IARC 1990).

Cancer Studies in Experimental Animals

Thiotepa administered by intraperitoneal injection caused lymphoma and/or leukemia (lymphocytic or granulocytic) in mice of both sexes and in male rats. It also caused benign lung tumors in mice of both sexes, cancer of the mammary gland and uterus in female rats, cancer of the skin or ear canal (squamous-cell carcinoma) in rats of both sexes and in male mice, and cancer of the preputial gland (squamous-cell carcinoma) in male mice (IARC 1975, 1990, NCI 1978). In male rats administered thiotepa by intravenous injection, cancer occurred at numerous tissue sites, including the abdominal cavity, mammary gland, blood vessels, bone marrow, lymphatic system, salivary glands, adrenal gland, and testis (IARC 1975, 1987, 1990).

Studies on Mechanisms of Carcinogenesis

Thiotepa and its major metabolite, tris(aziridinyl)phosphine oxide (also called TEPA or triethylenephosphoramidate) are direct alkylating agents with potent genotoxic activity in a wide variety of prokaryotic, lower eukaryotic, and mammalian *in vitro* and *in vivo* test systems. Thiotepa's ability to cause DNA damage, mutations, micronucleus formation, and/or chromosomal aberrations in somatic and germ cells from exposed rodents, rabbits, and nonhuman primates and chromosomal aberrations in peripheral-blood lymphocytes from treated humans is consistent with its being a genotoxic carcinogen (IARC 1990).

Properties

Thiotepa is an ethyleneimine alkylating agent (NCI 1978) that is a white crystalline solid with a faint odor at room temperature. It is soluble in water, alcohol, benzene, ether, and chloroform. It is un-

stable in light and in acidic solution, but stable in alkaline solutions (IARC 1990). Physical and chemical properties of thiotepa are listed in the following table.

Property	Information
Molecular weight	189.2 ^a
Melting point	51.5°C ^a
Log K _{ow}	0.53 ^b
Water solubility	190 g/L at 25°C ^b
Vapor pressure	0.00845 mm Hg at 25°C ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Thiotepa suppresses cell growth and division and was introduced in 1953 for use in cancer chemotherapy to treat lymphoma and a variety of solid and soft-tissue tumors. It was commonly used in cancer therapy until the early 1970s (only 3 kg of thiotepa was used in 1973). Although thiotepa has largely been replaced by the nitrogen mustards, it still has specific uses, particularly as a component of experimental high-dose chemotherapy regimens. Thiotepa was most effective in treating adenocarcinoma of the breast, ovary, and bladder, malignant lymphoma, bronchiogenic carcinoma, and Wilms' tumor. By the late 1980s, thiotepa was also used at high doses in combination chemotherapy with cyclophosphamide in patients with refractory malignancies treated with autologous bone transplantation (IARC 1975, 1990). As of 2009, thiotepa was used to treat a variety of cancers, including lymphoma and cancer of the bladder, ovary, breast, lung, and brain (MedlinePlus 2009).

Thiotepa was tested for use as an intermediate in the manufacture of polymeric flame retardants for cotton, and it was shown to be an effective insect chemosterilant. However, these uses were not developed for commercial application because of various problems associated with its application, toxicity, and environmental effects (IARC 1975).

Production

One U.S. company produced thiotepa in the early 1970s, but by 1990, it was produced only in Japan (IARC 1975, 1990). In 2009, thiotepa was produced by one manufacturer, in East Asia (SRI 2009), and was available from four U.S. suppliers (ChemSources 2009). Three U.S. pharmaceutical companies produced four drug products approved by the U.S. Food and Drug Administration that contained thiotepa as the active ingredient (FDA 2009). No data on current or past production or U.S. import or export volumes were found.

Exposure

Individuals are exposed to thiotepa during its use in cancer therapy. Thiotepa has been administered through various parenteral routes (e.g., intravenous, intramuscular, intrathecal, and intratumoral); generally, adjustment of the dosage is based on changes in leukocyte counts. Thiotepa is available in injectable form in solutions containing 15 or 30 mg per vial (FDA 2009). The initial dose typically is 5 to 40 mg (3 to 23 mg/m² of body surface area) administered at one- to four-week intervals; doses up to 75 mg/m² have been used in children. Daily doses in excess of 1,100 mg/m² have been used in high-dose therapy (IARC 1990).

Occupational exposure may occur among health-care professionals who prepare and administer thiotepa in cancer therapy and among workers involved in its formulation and packaging. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 11,452 workers, including 8,724 women, potentially were exposed to thiotepa (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Resource Conservation and Recovery Act

Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

Thiotepa is a prescription drug subject to labeling and other requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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References

- Adamson RH, Seiber SM. 1981. Chemically induced leukemia in humans. *Environ Health Perspect* 39: 93-103.
- ChemIDplus. 2009. *ChemIDplus Advanced*. National Library of Medicine. <http://chem.sis.nlm.nih.gov/chemidplus/chemidheavy.jsp> and select Registry Number and search on CAS number. Last accessed: 1/5/09.
- ChemSources. 2009. *Chem Sources - Chemical Search*. Chemical Sources International. <http://www.chemsources.com/chemonline.html> and search on thiotepa. Last accessed: 1/5/09.
- FDA. 2009. *The Electronic Orange Book*. U.S. Food and Drug Administration. <http://www.fda.gov/cder/ob/default.htm> and select Search by Active Ingredient and search on thiotepa. Last accessed: 1/5/09.
- HSDB. 2009. *Hazardous Substances Data Bank*. National Library of Medicine. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on CAS number. Last accessed: 1/5/09.
- IARC. 1975. Tris(1-aziridinyl)phosphine sulphide. In *Some Aziridines, N-, S-, and O-Mustards and Selenium*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 9. Lyon, France: International Agency for Research on Cancer. pp. 85-94.
- IARC. 1987. Tris(1-aziridinyl)phosphine sulphide (thiotepa). In *Overall Evaluations of Carcinogenicity*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, Supplement 7. Lyon, France: International Agency for Research on Cancer. pp. 368-369.
- IARC. 1990. Thiotepa. In *Pharmaceutical Drugs*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 50. Lyon, France: International Agency for Research on Cancer. pp. 123-141.
- MedlinePlus. 2009. *Thiotepa*. National Library of Medicine. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682821.html>. Last accessed: 11/23/09.
- NCI. 1978. *Bioassay of Thio-TEPA for Possible Carcinogenicity*. Technical Report Series no. 58. DHEW (NIH) Publication No. 78-1308. Bethesda, MD: National Institutes of Health. 168 pp.
- NIOSH. 1990. *National Occupational Exposure Survey (1981-83)*. National Institute for Occupational Safety and Health. Last updated: 7/1/90. <http://www.cdc.gov/noes/noes1/x4618sic.html>.
- SRI. 2009. *Directory of Chemical Producers*. Menlo Park, CA: SRI Consulting. Database edition. Last accessed: 1/5/09.